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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,885	11/10/2006	Marshall David Crew	0003.0553/PC32027A	1858

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EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/596,885	CREW ET AL.
	Examiner	Art Unit
	ALI SOROUSH	1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20 and 22-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20 and 22-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's response filed on 04/11/2011 to the Office Action mailed on 11/09/2010 is acknowledged.

Claim Status

Claims 20 and 22-34 are pending.

Claims 1-19 and 21 are cancelled.

Claim 20 is currently amended.

Claims 20 and 22-34 have been examined.

Claims 20 and 22-34 are rejected.

Priority

Priority to PCT/IB04/04260 filed on 12/20/2004 which claims priority to application 60/533848 filed on 12/31/2003 is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is modified from the previous Office Action as necessitated by amendment of the claims.

1. Claims 20-29 and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Infeld et al. (International Application Published Under the PCT WO 02/089835 A2, Published 11/14/2002) in view of Babcock et al. (European Patent Application 1027886 A2, Published 08/16/2000).

The claims are directed to solid composition comprising particles of at least 10% low-solubility amorphous drug, 30 to 65% poloxamer, and a at least 5% stabilizing polymer such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS). The claims are further directed to an anti-viral drug. The claims are further directed to the amount of HPMACS being present such that the MDC of the drug is increased at least 1.25 fold over a control.

Infeld et al. show a tablet comprising a kernel having 61.3% nelfinavir mesylate, 33.1% poloxamer 188, 3.4% microcrystalline cellulose, corn starch, and magnesium stearate. (page 12, example 5). Nelfinavir mesylate is an low-soluble, amorphous, hydrophobic antiviral drug. (page 1, Lines 5-28). The drug kernel is made by melt granulation process which results in the formation of particles. (page 6, Lines 7-15). The presence of poloxamer enhances the bioavailability of the drug. (page 2, Lines 15-16).

Infeld et al. lacks a teaching wherein the particles further comprise a stabilizing polymer such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

Babcock et al. show a solid dispersion of a low-solubility drug and a polymer. (abstract). The preferred polymer is cellulosic. (page 29, Lines 19-36). The most preferred polymer is the stabilizing polymer HPMCAS. (page 33, Lines 23-27, prior art claim 57). HPMC will stabilize amorphous low-soluble drugs so that they do not undergo change to crystalline form overtime during storage. (page 3, Lines 5-14). This dispersion provides an MCD and AUC of 1.25 fold over a control composition. (page 7, Lines 17-30). In preferred embodiment 30% HPMACS is present in an example dispersion (page 18, lines 20-25).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the composition of Infeld et al. by adding HPMCAS taught by Babcock et al. to the composition. One of ordinary skill in the art would have been motivated to do so in order to provide enhanced stability to the tablet formulation of Infeld et al. With regard to the instantly claimed glass transition temperature of the particle and drug as instantly claimed, it would be expected that the particles taught by Infeld et al. as modified by Babcock et al. would also possess this property. With regard to the instantly claimed method of making the composition, this is a product-by-process limitation that is not given patentable weight in a product claim.

Response to Applicant's Arguments

Applicant argues that Babcock et al. only mentions HPMCAS as not being within the scope of the invention and therefore does not cure the deficiencies of Infeld et al. Applicant's argument has been fully considered but found not to be persuasive. As noted in the previous Office Action Babcock et al. teaches that hydroxpropyl methyl cellulose acetate succinate (HPMCAS) is a stabilizing polymer useful in solid dispersion composition comprising the low-solubility drug (page 33, Lines 23-27). Further, Babcock et al. teach examples preferably utilizing HPMCAS in paragraph 0081and Table 1 (ex.no. 1, 5, c3, c5, c6, and c8). In paragraph 0058 Babcok et al. teach that HPMCAS is not within the scope of the invention when used **alone**. With regard to the new limitation that the composition comprise at least 10% drug, this limitation is met by Infeld et al. which teaches a composition of 61.3% drug (page 1, lines 5-28). With regard to the new limitation that composition comprises 30 to 65% poloxamer, Infeld et al. meets

this limitation with a teaching that poloxamer is present in an amount of 33.1% (page 1, lines 5-28). With regard to new limitation that the particles of low-solubility drug are homogenously distributed throught said poloxamer and stabilizing polymer, this limitation is made obvious by Babcock et al., which teaches that the low-solubility drug and stabilizing polymer form a solid dispersion (abstract). With regard to new limitation that the physically stability of the composition is 1.25 greater than one not utilizing a stabilizing polymer, this limitation is met by the teachings of Babcock et al. which teaches stabilization of the composition of 1.25 fold over controls not comprising stabilizing polymer (page 7, lines 17-30). Finally, with regard to the new limitation that the stabilizing polymer is present in an amount of at least 5%, Babcock et al. makes such an amount obvious teaching in a preferred embodiment adding HPMCAS in an amount of 30% (page 18, lines 20-25). Therefore, the rejection is maintained.

The following rejection is modified from the previous Office Action as necessitated by amendment of the claims.

2. Claims 20-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beyernick et al. (US Patent Application 2003/0163931 A1, Published 09/04/2003) in view of Infeld et al. (International Application Published Under the PCT WO 02/089835 A2, Published 11/14/2002).

The claims are directed to solid composition comprising particles of at least 10% low-solubility amorphous drug, 30 to 65% poloxamer, and at least 5% stabilizing polymer such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS). The

claims are further directed to [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxy-carbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbo-xylic acid ethyl ester. The claims are further directed to the amount of HPMACS being present such that the MDC of the drug is increased at least 1.25 fold over a control.

Beyernick et al. teach a method of making a homogeneous spray-dried solid amorphous dispersion. (title). A preferred particle comprises 25% [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxy-carbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbo-xylic acid ethyl ester and 75% HPMCAS. (paragraph 1255). This dispersion provides an MCD and AUC of 1.25 fold over a control composition. (paragraph 0047). The particle can also have a blend of polymers such as HPMCAS and poloxamer. (page 19, claim 19).

Bayernick et al. does not show a particle composition that comprises poloxamer.

Infeld et al. show a tablet comprising a kernel having 61.3% nelfinavir mesylate, 33.1% poloxamer 188, 3.4% microcrystalline cellulose, corn starch, and magnesium stearate. (page 12, example 5). Nelfinavir mesylate is an low-soluble, amorphous, hydrophobic antiviral drug. (page 1, Lines 5-28). The drug kernel is made by melt granulation process which results in the formation of particles. (page 6, Lines 7-15). The presence of poloxamer enhances the bioavailability of the drug. (page 2, Lines 15-16).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the composition of Bayernick et al. by adding poloxamer as taught by Infeld et al. One would have been motivated to do so since Infeld et al. teach that the addition of poloxamer would enhance the bioavailability of the active ingredient.

With regard to the instantly claimed glass transition temperature of the particle and drug as instantly claimed, it would be expected that the particles taught by Bayernick et al. as modified by Infeld et al. would also possess this property.

Response to Applicant's Arguments

Applicant argues that Infeld et al. does not disclose the relative amounts of drug, poloxamer, and stabilizing agent in the composition. Applicant's argument has been fully considered but found not to be persuasive. Infeld et al. is only relied upon to show that it would have been obvious to add a poloxamer to the composition of Bayernick et al. Bayernick et al. teaches the new limitation, that the composition comprises at least 10% drug, wherein the drug of Bayernick et al. is present in a concentration of 25% (paragraph 1255). With regard to the new limitation regard to concentrations of poloxamer and the stabilizing polymer, 30-65% poloxamer and at least 5% stabilizing polymer, the combination of Bayernick et al. and Infeld et al. makes this obvious to one of ordinary skill in the art at the time of the instant invention. Bayernick et al. teach that a mixture of HPMCAS and poloxmer can be used and in preferred embodiment 75% HPMCAS is present. Infeld et al. teach in a preferred embodiment the utilization of 33.1% poloxamer. It would have been obvious to one of ordinary skill in the art at the time of the instant invention wanting to making a mixture of poloxamer and HPMACS to use 33.1% poloxamer and 41.9% HPMCAS, which reads on the instant claim limitations.

Applicant also argues that Infeld et al. does not teach particles consist of a solid solution of the drug is homogeneously distributed through the poloxamer and stabilizing polymer. Applicant's argument has been fully considered but found not to be persuasive. Infeld et al. is only relied upon to show that it would have been obvious to add a poloxamer to the composition of Bayernick et al. Bayernick et al. teaches the new limitation, by teaching a homogeneous spray-dried solid amorphous dispersion (title). Therefore, the rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached on M-F (9am-6pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on (571)272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/A. S./
Examiner, Art Unit 1617

/KARLHEINZ R SKOWRONEK/
Primary Examiner, Art Unit 1631

June 17, 2011